

# Use of Aquaporins as Biomarkers in Drowning Cases: Review Paper

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## Abstract

Drowning remains a major challenge in forensic practice, particularly in distinguishing whether immersion occurred before or after death and in differentiating between freshwater and saltwater drowning. Traditionally, the diatom test has been the primary tool for confirming drowning, but its limitations in sensitivity and specificity highlight the need for alternative approaches. Aquaporins (AQPs), a family of water channel proteins, have emerged as potential biomarkers in drowning investigations due to their role in water transport and osmotic regulation. This review consolidates findings from published studies that employed immunohistochemistry (IHC) and immunofluorescence (IF) to evaluate the expression of AQP subtypes (AQP2, AQP4, AQP5) in lung, kidney, and brain tissues. Evidence indicates that hypo-expression of AQP5 is associated with freshwater drowning, while AQP2 and AQP4 show distinct patterns useful in differentiating drowning types. By highlighting these results, the study emphasizes that aquaporin markers may complement or even improve upon the diatom test, offering a promising diagnostic tool in forensic investigations of drowning deaths.

**Keywords:** Aquaporins, drowning, biomarkers, diatom test, immunohistochemistry, forensic pathology

## Introduction

Drowning is recognized as one of the leading causes of accidental death worldwide. The World Health Organization (WHO) reports that nearly 236,000 people lose their lives to drowning each year, representing around 0.7% of all global deaths. <sup>(1)</sup> The problem is particularly pronounced in low- and middle-income countries, where open water bodies are common and preventive measures are often limited. In India, with its rivers, lakes, wells, and coastal regions, drowning continues to present both a public health and a forensic challenge.

From a forensic perspective, diagnosing drowning is notoriously complex. Unlike firearm injuries or poisoning, which often leave clear and specific traces, drowning does not have a single pathognomonic sign. Instead, forensic practitioners must rely on a constellation of findings—froth at the mouth, waterlogged lungs, or fluid in the stomach—that, while suggestive, are not exclusive to drowning. Similar changes may occur in cases of cardiac failure, epilepsy, or other forms of asphyxia. As a result, the determination of drowning often requires a careful balance of autopsy findings, crime scene investigation, and circumstantial evidence.<sup>(2)</sup>

## Types of Drowning and Pathological Changes

Drowning can present in different forms, such as wet drowning, dry drowning, secondary drowning, and hydrocution, each with distinct physiological mechanisms. These variations influence the pathological findings observed during forensic examination. For instance, the type of

water (freshwater or seawater) affects fluid and electrolyte balance, leading to characteristic internal changes, while external features such as froth, washerwoman's skin, or cutis anserina may further assist in identification.<sup>(3)</sup> Thus, by correlating the type of drowning with the expected external and internal manifestations, as outlined in Tables 1 and 2, forensic pathologists can better interpret the cause and manner of death in suspected drowning cases.

**Table 1. Types of drowning<sup>(5,6)</sup>**

Type	Description	Mechanism/Physiology	Time to Death	Key Forensic Notes
Wet Drowning (Freshwater) <sup>(4)</sup>	Most common; water enters lungs.	Hypotonic water absorbed → hemodilution → RBC lysis, electrolyte imbalance, surfactant loss → ↓ lung compliance → cardiac arrhythmia.	2-3 minutes	Lungs heavy & waterlogged; electrolyte imbalance clues.
Wet Drowning (Seawater) <sup>(4)</sup>	Water enters lungs.	Hypertonic seawater draws plasma into alveoli → pulmonary edema, hemoconcentration, ↑ salt levels → cardiac failure.	4-5 minutes	Marked pulmonary edema; serum salt rise.
Dry Drowning	Water stimulates larynx but does not reach lungs.	Laryngospasm → airway obstruction → asphyxia.	Rapid	No water in lungs; death due to spasm.
Secondary Drowning (Post-immersion)	Occurs after apparent survival.	Delayed pulmonary complications: anoxia, acidosis, brain injury, bronchopneumonia.	Hours-days	Important medico-legally in revived victims who later die.
Hydrocution (Immersion Syndrome)	Sudden death on immersion in cold water.	Vagal inhibition due to nerve stimulation → cardiac arrest.	Instant	Seen in cold water immersion; minimal autopsy findings.

**Table 2. External and Internal Findings in Drowning<sup>(7)</sup>**

Category	Typical Findings
External	<ul style="list-style-type: none"> <li>- Wet hair, clothing, and skin.</li> <li>- Pale, cold, and clammy appearance.</li> <li>- Lividity: pink in freshwater, darker in saltwater (depending on time submerged).</li> <li>- Cutis anserina ("gooseflesh"), caused by contraction of tiny skin muscles.</li> <li>- Cadaveric spasm: tightly holding weeds, sand, or objects from the water.</li> <li>- "Washerwoman's" hands and feet after prolonged immersion.</li> <li>- Persistent froth at the nose and mouth, sometimes blood-tinged.</li> </ul>

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Internal	<ul style="list-style-type: none"> <li>- Airways filled with fine froth and water.</li> <li>- Lungs heavy and waterlogged, often showing rib imprints (emphysema aquosum).</li> <li>- Paltauf's hemorrhages: pinpoint bleeding beneath the pleura.</li> <li>- Fluid, diluted blood due to water inhalation.</li> <li>- Sand, mud, or water in the respiratory passages.</li> <li>- Fluid in the middle ear cavity.</li> </ul>
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### Medico-legal challenges

In the courtroom, the key forensic question is whether the individual died **before** entering the water or was submerged **after death**. This distinction has profound implications for determining whether the case is accidental, suicidal, or homicidal.<sup>(8)</sup>

- **Accidental drowning** is the most common, often involving children, elderly individuals, or intoxicated persons who accidentally fall into water bodies.
- **Suicidal drowning** is relatively more frequent in women and may involve deliberate acts, such as carrying weights or selecting secluded locations.
- **Homicidal drowning** is rare but critical to identify. It may be accompanied by injuries, intoxication, or restraint that suggest foul play.

Estimating the **time since death** adds another layer of complexity. Fresh froth and bright lividity may be seen in early stages, but as decomposition progresses, these signs are obscured. Similarly, immersion changes like skin wrinkling can help, but they only provide rough timelines.

Bodies recovered from polluted waters or in advanced decomposition pose additional challenges, as conventional autopsy findings degrade rapidly. These limitations underscore the need for more robust diagnostic tools that can withstand variable environmental conditions.

### Diatoms as a Biomarker

To address the shortcomings of traditional autopsy, forensic science has long relied on the **diatom test** as an auxiliary tool in drowning diagnosis.<sup>(9)</sup> **Underlying principle**-Diatoms are

tiny unicellular algae with walls made of silica. During drowning, water inhaled into the lungs may allow diatoms to cross the alveolar barrier and spread through the bloodstream to distant organs, including the liver, kidneys, brain, and bone marrow. Their presence in these tissues provides strong support for **ante-mortem drowning**, since post-mortem immersion does not typically permit such circulation.<sup>(10)</sup>

### Forensic Utility

- Because diatom species vary between water bodies, comparing diatoms recovered from tissues with those from the suspected site of drowning can help confirm both the cause and the location of death.
- In India, several regional studies highlight this potential. For instance, the diatom flora of Kerala's backwaters differ markedly from those in inland rivers, helping narrow down the scene of drowning. Similarly, research along the Ganga basin has shown seasonal variation in diatom species, making it possible to link drowning cases to specific stretches of the river. Despite its usefulness, the diatom test is not without drawbacks; False positives can occur due to contamination of samples during collection or analysis. In decomposed bodies, diatoms may be difficult to recover. Some water bodies, especially those with low nutrient levels, contain few diatoms, limiting the sensitivity of the test.

### Aquaporins as Potential Biomarkers in Drowning Cases

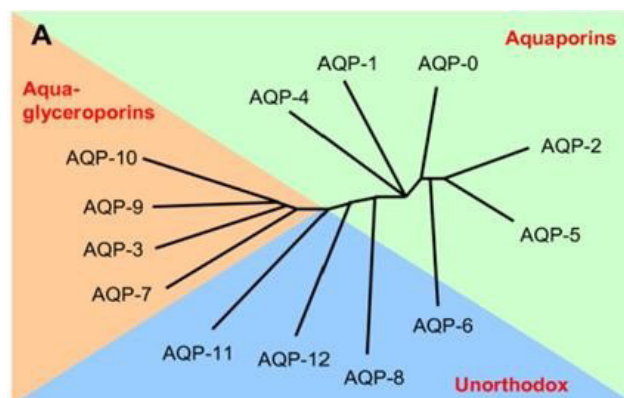
Over the years, significant advancements have been made in forensic pathology with the

development of biomarkers that aid in accurate diagnosis and identification of cause of death. Traditional biomarkers such as enzymes, proteins, and later DNA profiling have played a crucial role in forensic investigations. (11)With the advent of molecular biology, newer and more sensitive biomarkers have emerged, offering higher reliability in differentiating between causes and manners of death. For example, genetic markers, mitochondrial DNA,<sup>(12)</sup> and proteomic signatures have been increasingly applied in forensic science to establish identity and pathological processes with greater certainty.

In line with these advancements, research has highlighted that aquaporins (AQPs), a family of water channel proteins, could serve as promising biomarkers in forensic pathology, particularly in drowning cases. (13)The aim of this review is to explore the potential of aquaporins as biomarkers for differentiating types of drowning, such as freshwater versus saltwater drowning, thereby providing a more confirmatory tool for forensic identification.

Aquaporins are integral membrane proteins that facilitate the transport of water and, in some cases, small solutes across cell membranes. The human body possesses **13 types of aquaporins (AQP0–**

**AQP12)**, classified into three main groups: orthodox aquaporins (AQP0, 1, 2, 4, 5, 6, 8), aquaglyceroporins (AQP3, 7, 9, 10), and unorthodox aquaporins (AQP11, 12). (14)Each type shows organ-specific expression—for example, AQP0 in the lens of the eye, AQP1 in the kidney and lungs, AQP3 in the gastrointestinal tract, and AQP4 in the central nervous system.



The family tree of aquaporins (15)

Among these, **AQP2, AQP4, and AQP5** have drawn special attention in drowning studies due to their roles in water balance, lung fluid regulation, and brain water homeostasis. Studies suggest that differences in the expression and distribution of these aquaporins may help forensic experts distinguish between freshwater drowning (FWD) and saltwater drowning (SWD).

**Table 3. Aquaporins Relevant to Drowning Cases**

Aquaporin	Primary Location	Physiological Role	Forensic Relevance in Drowning
AQP2 <sup>(16)</sup>	Kidney (collecting duct principal cells, apical plasma membrane, intracellular vesicles)	Vasopressin-regulated water permeability; controls water reabsorption in kidneys	Altered expression may indicate water imbalance in fresh water vs. salt water drowning
AQP4 <sup>(17)</sup>	Brain (astrocytes, ependymal cells, perivascular end feet), spinal cord, optic nerve	Regulates brain water homeostasis; involved in bidirectional fluid exchange in CNS	Overexpression linked to cerebral edema, useful in identifying drowning-induced brain water changes
AQP5 <sup>(17)</sup>	Lungs (epithelial cells including alveolar type-1 cells, bronchial epithelium), renal cortex	Involved in fluid handling in lungs and airways; associated with lung injury	Expression differences may help distinguish between FWD and SWD due to pulmonary fluid imbalance

## Objective of This Study

This review paper aims to explore the role of aquaporins as potential biomarkers in drowning cases. By assessing their organ-specific expression, the study highlights how aquaporins may help differentiate between fresh water and salt water drowning, serving as a supportive tool for confirmation in forensic investigations.

## Material and Methodology

In this review, the methodological framework followed by researchers investigating the role of aquaporins in drowning cases generally included three major stages. First, case grouping was performed by categorizing subjects into freshwater drowning (FWD), saltwater drowning (SWD), and non-drowning controls (CTR), which included cases such as cardiac deaths, blunt trauma, fire fatalities, poisoning, and sepsis. Second, sample collection was carried out during autopsy, where lungs, kidneys, and brain tissues were harvested. These tissue blocks were preserved in 10% formalin, embedded in paraffin, and processed within a defined

post-mortem interval that varied across studies (ranging from 0.5–30 hours to 24–72 hours). Third, laboratory analyses were conducted, beginning with histological examination to observe tissue architecture and pathological changes. This was followed by immunohistochemistry (IHC),<sup>(18)</sup> where thin paraffin sections underwent antigen retrieval, blocking of non-specific binding, and incubation with primary aquaporin antibodies. Secondary enzyme- or fluorescence-conjugated antibodies were then applied, and results were visualized either by enzymatic staining (visible as brown deposits under light microscopy) or by fluorescence microscopy. In addition, immunofluorescence (IF) and double-color IF techniques were employed to study co-localization of aquaporins with specific cellular markers, such as GFAP for glial cells, and digital merging of signals was used for detailed analysis.<sup>(19)</sup> Finally, morphometric analysis allowed quantitative assessment of aquaporin expression in terms of intensity, localization, and distribution across the tissue sections, thereby providing measurable data for comparison between drowning types and control cases.

**Table 4. Experiments on aquaporins.**

Experiment	Subjects & Groups	Organ(s) Studied	Methods Applied	Antibodies/ Markers Used	Key Features
Exp 1: AQP5 in Lung & Kidney <sup>(20)</sup>	<ul style="list-style-type: none"> <li>• 30 drowning cases (15 FWD, 15 SWD)</li> <li>• 17 controls (6 cardiac, 4 polytrauma, 1 overdose, 6 gunshot)</li> <li>• All males, 20–24 yrs • Autopsy: 24–72 h post-mortem</li> </ul>	<ul style="list-style-type: none"> <li>• Lung</li> <li>• Kidney</li> </ul>	<ul style="list-style-type: none"> <li>• Histology • IHC</li> </ul>	<ul style="list-style-type: none"> <li>• AQP-5 (Novus Biologicals NBP2-39043)</li> </ul>	<ul style="list-style-type: none"> <li>• Formalin-fixed, paraffin-embedded</li> <li>• Clear expression differences in drowning vs controls</li> </ul>
Exp 2: AQP2 in Kidney <sup>(21)</sup>	<ul style="list-style-type: none"> <li>• 51 drowning (23 FWD, 24 SWD; 30 ♂, 21 ♀) • 19 controls (5 blunt trauma, 5 fire, 2 drug, 2 brain injury, 1 sharp, 1 asphyxia, 1 MI, 1 diabetes, 1 sepsis)</li> </ul>	<ul style="list-style-type: none"> <li>• Kidney</li> </ul>	<ul style="list-style-type: none"> <li>• IHC, Morphometric analysis</li> </ul>	<ul style="list-style-type: none"> <li>• Rabbit anti-human AQP1 • Goat anti-human AQP2 • Rabbit anti-human AQP4</li> </ul>	<ul style="list-style-type: none"> <li>• AQP2 expression in kidney</li> <li>• Key for differentiating drowning types</li> </ul>

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Exp 3: AQP4 in Brain <sup>(22)</sup>	<ul style="list-style-type: none"> <li>• 70 cases (22 FWD, 26 SWD, 22 controls)</li> <li>• Controls: 6 fire, 3 shock, + single cases (brain injury, sharp, CO, drug, hypothermia, asphyxia, SAH, MI, sepsis, etc.)</li> <li>• 41 ♂, 29 ♀, age: 5 mo–90 yrs</li> <li>• Post-submersion: 0.5–30 h</li> </ul>	<ul style="list-style-type: none"> <li>• Brain (parieto-occipital lobe, arterial boundary zone)</li> </ul>	<ul style="list-style-type: none"> <li>• IHC</li> <li>• Double-color IF</li> <li>• Morphometry</li> </ul>	<ul style="list-style-type: none"> <li>• Rabbit anti-human AQP1</li> <li>• Rabbit anti-human AQP4</li> <li>• GFAP marker</li> </ul>	<ul style="list-style-type: none"> <li>• AQP4 localized in glial cells</li> <li>• Double-IF showed cerebral edema patterns in drowning</li> </ul>
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### Result and Discussion

The present findings highlight distinct patterns of aquaporin expression in different tissues depending on the type of drowning.

#### Lung Tissue (AQP5)

Lung samples revealed a **significant hypo-expression of AQP5 in FWD cases** compared to SWD and CTR. This supports the hypothesis that in freshwater drowning, the **hypotonic medium drives water absorption from alveoli into the bloodstream**,<sup>(23)</sup> activating AQP5 as a major pathway for water transport across type I pneumocytes. The reduced expression of AQP5 appears to be a compensatory response to limit further water influx. This aligns with Hayashi et al.'s results from both human and murine models. In contrast, **SWD cases did not differ significantly from controls**, suggesting that hypertonic saltwater inhalation does not provoke the same downregulation mechanism.

#### Kidney Tissue (AQP5, AQP1, AQP2, AQP4)

In kidneys, **AQP5 expression was localized to the cortical collecting duct system**. The pattern mirrored lung findings, showing **lower expression in FWD** compared to SWD and CTR. This observation indicates that renal AQP5 may act as an **osmo-sensor**, responding rapidly to plasma hypo-osmolarity during freshwater drowning. Interestingly, while AQP1 and AQP4 expression remained stable across all groups, **AQP2 showed enhanced expression in SWD**, likely due to the hyperosmotic stress, whereas FWD showed reduced levels compared to CTR.

#### Brain Tissue (Astrocytes, AQP1 and AQP4)

In brain tissue, immunofluorescence revealed **AQP1-positive astrocytes** without significant differences across the groups, suggesting a stable role in water balance. However, **AQP4-positive astrocytes demonstrated group-specific differences**, indicating a more dynamic regulation of this channel in response to drowning medium.

**Table 5. Result of experiment** <sup>(20-22)</sup>

Experiment	Target Aquaporin	Tissue	Observation
Exp-1	AQP5	Lung (pneumocytes, bronchial epithelium) & Kidney (cortical collecting duct)	<b>Hypo-expression in FWD</b> compared to SWD & CTR. No significant difference between SWD and CTR.

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Exp-2	AQP1, AQP2, AQP4	Kidney (proximal tubules, collecting duct)	AQP1 & AQP4: no difference across groups. AQP2: <b>Enhanced in SWD</b> , reduced in FWD, normal in CTR.
Exp-3	AQP1 & AQP4 (astrocytes)	Brain (astrocytes, GFAP+)	AQP1-positive astrocytes: no difference across groups. AQP4-positive astrocytes: <b>Distinct differences observed</b> , higher in SWD.

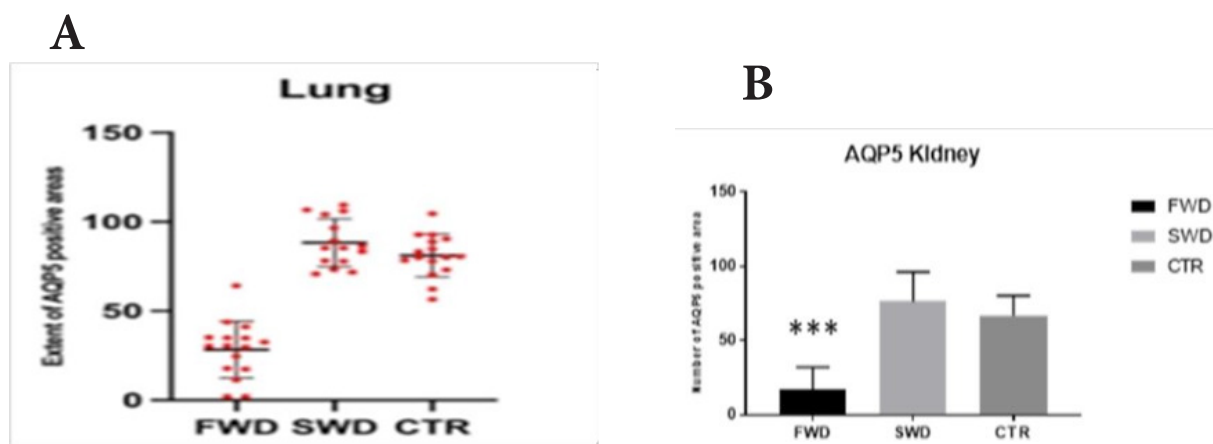
### Overall Interpretation

The results collectively show that **aquaporins, particularly AQP5, exhibit differential expression in drowning cases**, with FWD associated with hypo-expression and SWD with either stable or enhanced expression. These patterns can provide valuable forensic insights into the type of drowning. Moreover, the consistent findings across multiple tissues (lung, kidney, brain) strengthen the argument for considering **aquaporin profiling as a potential biomarker in forensic drowning investigations**.

### Comparative Overview with Previous Literature

The majority of reviewed studies agree that AQP5 (lungs and kidneys) and AQP4 (brain)

show consistent, reproducible differences between freshwater and saltwater drowning. However, discrepancies exist regarding the magnitude of AQP2 changes, which may be influenced by methodological differences (e.g., IHC vs. IF techniques), post-mortem interval, or comorbid conditions. Furthermore, while earlier forensic approaches relied on diatom testing or electrolyte shifts, aquaporin profiling offers a molecular-level perspective that is less affected by decomposition. Nonetheless, studies emphasize the need for standardization of protocols and validation across larger case cohorts.



A- In lungs, *in pneumocytes and bronchial epithelial cell hypo-expression of AQP5 in FWD than in SWD and CTR.*

B- In KIDNEY, they found AQP5 in cortical collecting duct system. The results were like lungs, *hypo-expression of AQP5 in FWD when compared to SWD and CTR.*<sup>(23)</sup>

## Conclusion

Aquaporins have emerged as promising biomarkers in the field of forensic pathology, particularly in the differentiation of freshwater drowning (FWD) and saltwater drowning (SWD) cases. The reviewed studies demonstrated that intrarenal AQP2 and AQP5, intrapulmonary AQP5, and intracerebral AQP4 play significant roles in distinguishing drowning subtypes, with AQP4-positive astrocytes being fewer in SWD than in FWD and controls. Immunohistochemical and immunofluorescence analyses further confirmed that aquaporin expression is not influenced by the post-submersion interval, reinforcing their stability and reliability in forensic examinations. The selective permeability of aquaporins for water and certain solutes provides a physiological basis for their application, as they regulate osmotic balance, cellular hydration, and volume, processes that undergo distinct changes when cells are exposed to freshwater or saltwater environments.

However, despite their potential, several limitations remain. Aquaporin expression can be influenced by environmental factors such as temperature, pH, and osmotic conditions, which may complicate interpretation. Limited tissue specificity also poses challenges, as aquaporins are expressed across multiple organs, making it difficult to pinpoint precise tissue origins. Additionally, a lack of standardized protocols and guidelines for aquaporin detection hinders their consistent application in routine forensic practice. Furthermore, disease states, drug intoxications, and pathological conditions may alter aquaporin expression, creating overlaps with drowning-related findings.

Nevertheless, the accumulated research strongly suggests that aquaporins, especially AQP2, AQP4, and AQP5, provide valuable supplementary evidence in the diagnosis of drowning. Their ability to indicate water type exposure, combined with morphometric and immunohistochemical approaches, makes them useful markers in cases where classical drowning signs are absent due to decomposition or environmental factors. While

aquaporins alone may not serve as definitive diagnostic markers, when combined with other forensic parameters and biomarkers, they significantly enhance the accuracy and reliability of drowning investigations. Thus, aquaporins hold great potential as emerging forensic tools, warranting further research and standardization for their broader adoption in forensic science.

**Ethical Clearance :** NA

**Conflict of Interest :** NA

**Source of Funding :** NA

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